Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation

The new england journal *of* medicine. 2023

Atrial fibrillation is typically diagnosed by means of electrocardiography in patients with symptoms

Clinical atrial fibrillation is a leading cause of stroke, particularly among older persons.

Vitamin K antagonists and direct-acting oral anticoagulants reduce the risk of stroke among patients with clinical atrial fibrillation while increasing the risk of bleeding

Approximately 20 years ago , pacemakers and implantable cardioverter – defibrillators that could continuously detect and characterize atrial arrhythmias were widely introduced. It was quickly observed that short episodes of asymptomatic atrial fibrillation were common, even in patients with no other evidence of clinical atrial fibrillation.

We reported that subclinical atrial fibrillation was present in more than one third of older patients with hypertension who had received a pacemaker and was associated with an increased risk of ischemic stroke or systemic embolism

However, the absolute increase in stroke risk with subclinical atrial fibrillation was 1 percentage point per year, approximately half the risk increase observed among patients with clinically detected atrial fibrillation.

Given the bleeding risk associated with oral anticoagulants, particularly among older persons, the role of oral anticoagulation in the management of subclinical atrial fibrillation is uncertain.

Apixaban is a direct-acting oral anticoagulant that has an excellent risk–benefit profile for stroke prevention among patients with clinical atrial fibrillation

Eligible patients

had subclinical atrial fibrillation that was detected by an implanted pacemaker, defibrillator, or cardiac monitor

with at least one episode lasting 6 minutes or longer but no episodes lasting longer than 24 hours.

had a CHA2DS2-VASc score of 3 or higher (scores range from 0 to 9, with higher scores indicating a higher risk of stroke).

minimum age of participants to 55 years

allowed for the enrollment of patients who were 75 years of age or older or who had a history of stroke without other risk factors.

Patients were excluded

✓ they had a history of clinical atrial fibrillation, an ongoing indication for oral anticoagulation

✓ a history of uncorrected major bleeding in the previous 6 months

✓ a creatinine clearance of less than 25 ml per minute

✓ The concurrent use of open label aspirin was allowed but discouraged, whereas the use of open-label dual antiplatelet therapy was prohibited.

Trial Interventions

Patients underwent randomization in

a double blind , double-dummy fashion to receive either

apixaban at a dose of 5 mg twice daily (reduced to 2.5 twice daily as indicated by product labeling) or aspirin at a dose of 81 mg daily.

If subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation developed, the apixaban or aspirin was stopped, follow-up was continued, and treatment with an open-label anticoagulant was initiated.

The trial drug was also **stopped** as specified in the protocol if the creatinine clearance fell below 25 ml per minute

The primary efficacy outcome

composite of stroke and systemic embolism

was assessed in the intention-to-treat population (all the patients who had undergone randomization), with censoring of follow-up once subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation developed.

on-treatment population (all the patients who had undergone randomization and received at least one dose of the assigned trial drug), with follow-up censored 5 days after permanent discontinuation of trial medication for any reason.

The primary safety outcome

was major bleeding

Statistical Analysis

We calculated that the enrollment of 4000 patients would provide the trial with a power of 80% to detect a relative reduction of 35% in the risk of stroke or systemic embolism in the apixaban group.

We performed Kaplan-Meier analysis to compare the rate of primary outcome events in the two groups and used a Cox proportional-hazards model to investigate variable effects

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N=2015)	Aspirin (N=1997)	Total (N=4012)
Age — yr	76.9±7.6	76.7±7.7	76.8±7.6
Female sex — no. (%)	719 (35.7)	728 (36.5)	1447 (36.1)
CHA_2DS_2-VASc score†			
Mean	3.9±1.1	3.9±1.1	3.9±1.1
Score ≥4 — no. (%)	1220 (60.5)	1214 (60.8)	2434 (60.7)
History of hypertension — no. (%)	1643 (81.5)	1626 (81.4)	3269 (81.5)
History of coronary artery disease — no. (%)	731 (36.3)	754 (37.8)	1485 (37.0)
Peripheral arterial disease — no. (%)	168 (8.3)	166 (8.3)	334 (8.3)
Diabetes mellitus — no. (%)	583 (28.9)	584 (29.2)	1167 (29.1)
History of heart failure — no. (%)	550 (27.3)	587 (29.4)	1137 (28.3)
History of stroke, systemic embolism, or TIA — no. (%)	180 (8.9)	181 (9.1)	361 (9.0)
Race or ethnic group — no. (%)‡			
White European	1897 (94.1)	1881 (94.2)	3778 (94.2)
Black African	42 (2.1)	46 (2.3)	88 (2.2)
Native Latin	8 (0.4)	12 (0.6)	20 (0.5)
South Asian	7 (0.3)	10 (0.5)	17 (0.4)
Native North American or Pacific Islander	10 (0.5)	4 (0.2)	14 (0.3)
Other	51 (2.5)	44 (2.2)	95 (2.4)
Baseline antiplatelet use — no. (%)			
Aspirin	1165 (57.8)	1137 (56.9)	2302 (57.4)
Other single antiplatelet agent	77 (3.8)	81 (4.1)	158 (3.9)
Dual antiplatelet therapy	67 (3.3)	70 (3.5)	137 (3.4)
Creatinine clearance — ml/min	70.8±26.7	72.1±30.6	71.4±28.7
Weight — kg	82.5±18.3	82.9±18.1	82.7±18.2
History of major bleeding >6 mo before enrollment — no. (%)	50 (2.5)	47 (2.4)	97 (2.4)
Blood pressure — mm Hg			
Systolic	135.0±18.9	135.0±18.7	135.0±18.8
Diastolic	75.4±10.4	75.5±10.4	75.5±10.4
Device type — no. (%)			
Pacemaker	1414 (70.2)	1370 (68.6)	2784 (69.4)
ICD	270 (13.4)	284 (14.2)	554 (13.8)
CRT-ICD or CRT pacemaker	228 (11.3)	237 (11.9)	465 (11.6)
ICM	103 (5.1)	106 (5.3)	209 (5.2)
No. of episodes of SCAF lasting ≥6 min during the 6 mo before randomization — no./total no. (%)			
0	354/2014 (17.6)	356/1997 (17.8)	710/4011 (17.7)
1 to 5	1283/2014 (63.7)	1274/1997 (63.8)	2557/4011 (63.7)
6 to 50	334/2014 (16.6)	328/1997 (16.4)	662/4011 (16.5)
>50	43/2014 (2.1)	39/2014 (2.0)	82/2011 (4.1)

Table 1. (Continued.)

Characteristic	Apixaban (N=2015)	Aspirin (N=1997)	Total (N=4012)
Longest episode of SCAF in past 6 mo — no./total no. (%)			
No episodes	317/2012 (15.8)	315/1995 (15.8)	632/4007 (15.8)
<6 Min	42/2012 (2.1)	43/1995 (2.2)	85/4007 (2.1)
6 Min to <1 hr	535/2012 (26.6)	497/1995 (24.9)	1032/4007 (25.8)
1 to <6 Hr	681/2012 (33.8)	743/1995 (37.2)	1424/4007 (35.5)
6 to <12 Hr	287/2012 (14.3)	264/1995 (13.2)	551/4007 (13.8)
12 to 24 Hr	150/2012 (7.5)	133/1995 (6.7)	283/4007 (7.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CRT denotes cardiac resynchronization therapy, ICD implantable cardioverter–defibrillator, ICM insertable cardiac monitor, SCAF subclinical atrial fibrillation, and TIA transient ischemic attack.

† CHA_2DS_2-VASc scores (an assessment of the risk of stroke among patients with atrial fibrillation) range from 0 to 9, with higher scores indicating a higher risk of stroke.

‡ Race and ethnic group were reported by the patient.

Results

Between May 7, 2015, and July 30, 2021, a total of 4012 patients underwent randomization, 2015 to the apixaban group and 1997 to the aspirin group

A total of 51 patients (26 in the apixaban group and 25 in the aspirin group) did not receive at least one dose of a trial medication

Apixaban or aspirin was permanently discontinued during follow-up owing to the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation in 490 patients (24.3%) in the apixaban group and 476 patients (23.8%) in the aspirin group.

The median time from randomization to discontinuation of a trial medication owing to the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation was 18.3 months

Trial medication was discontinued for other reasons in 687 patients (34.1%) in the apixaban group and 697 patients (34.9%) in the aspirin group.

During follow-up, death occurred in 457 patients (22.7%) in the apixaban group and in 438 patients (21.9%) in the aspirin group

61 patients in the apixaban group and 57 patients in the aspirin group were withdrawn or were lost to follow-up without a final visit

The median time from randomization to discontinuation of a trial medication owing to the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation was 18.3 months

The mean (±SD) duration of follow-up was 3.5±1.8 years for the intention-to-treat analysis and 2.5±1.8 years for the on-treatment analysis.

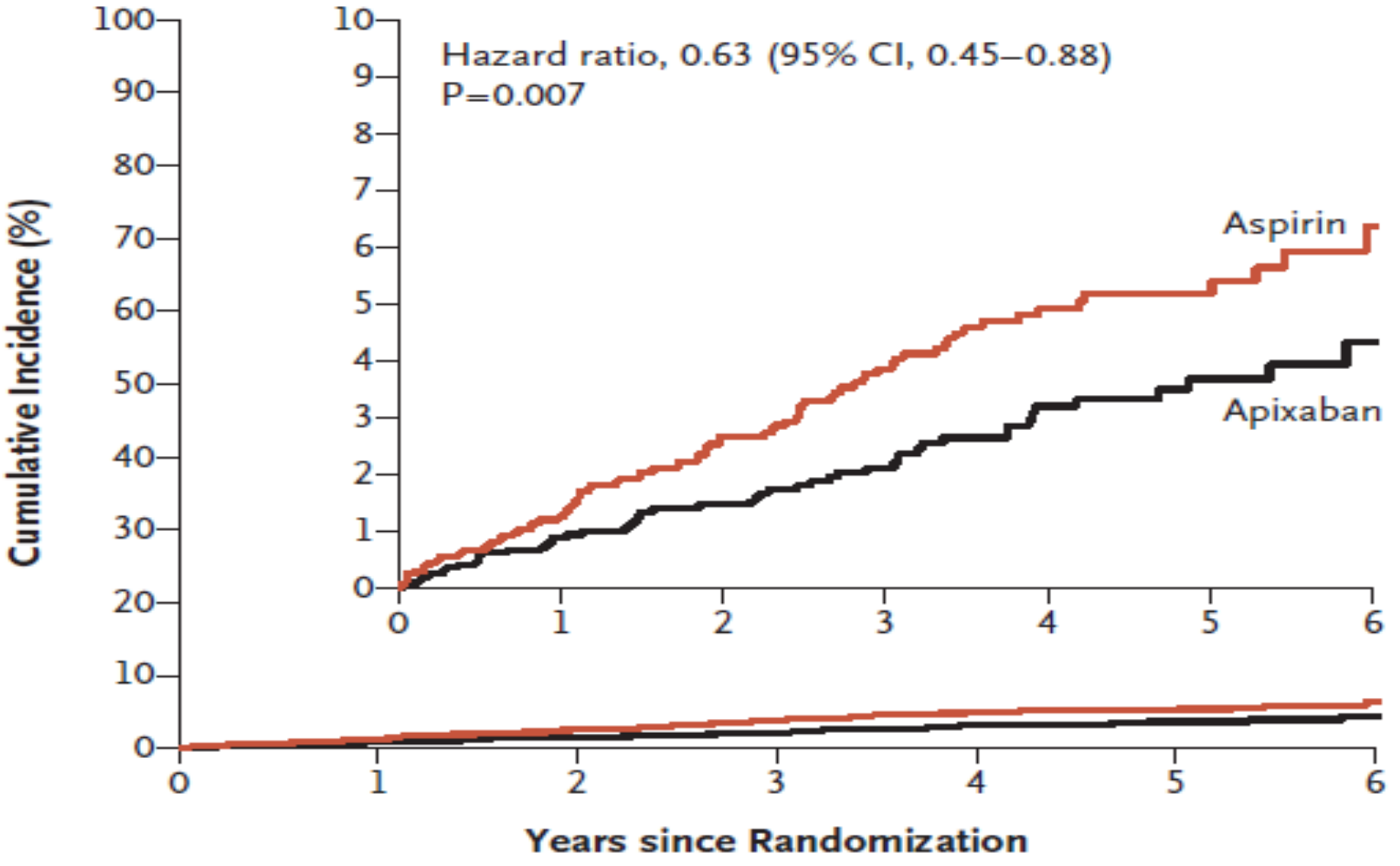

Figure 1. Stroke or Systemic Embolism (Primary Efficacy Outcome).

Intention-to-Treat Analysis

Stroke or systemic embolism (primary efficacy outcome) occurred in 55 patients assigned to receive apixaban (0.78% per patient-year) and 86 patients assigned to receive aspirin (1.24% per patient-year) (hazard ratio, 0.63; 95% confidence interval [CI], 0.45 to 0.88; P = 0.007).

Similar between-group differences were observed in ischemic stroke

Stroke severity was assessed as being disabling or fatal (score on the modified Rankin scale, 3 to 6) in 18 of 55 strokes (33%) in the apixaban group and in 36 of 84 strokes (43%) in the aspirin group

The risk of disabling or fatal stroke was lower by 49% with apixaban than with aspirin (hazard ratio, 0.51; 95% CI, 0.29 to 0.88).

Deaths were similar in number between the two groups. Major bleeding in the intention-to-treat population occurred more often with apixaban than with aspirin

The risk of the composite of stroke, systemic embolism, or death from cardiovascular causes was similar for patients assigned to receive apixaban and those assigned to receive aspirin

An intention- to-treat analysis that did not censor data for patients after the development of subclinicalatrial fibrillation lasting longer than 24 hours or clinical atrial fibrillation showed results similar to those of the primary analysis .No significant subgroup interactions were seen for any of the prespecified subgroups of interest.

On-Treatment Analysis

The risk of major bleeding was 1.71% per patient year with apixaban and 0.94% per patient-year with aspirin

Table 2. Clinical Outcomes (Intention-to-Treat Population).*

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*	
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)
Severity according to score on modified Rankin scale‡					
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)
Systemic embolism	0		2	0.03	NA
Stroke, TIA, or systemic embolism§	82	1.17	107	1.56	0.75 (0.56–1.00)
Stroke, systemic embolism, or death from cardiovascular causes	148	2.10	171	2.47	0.85 (0.68–1.06)
Stroke, myocardial infarction, systemic embolism, or death	419	6.01	418	6.10	0.98 (0.86–1.12)
Myocardial infarction	37	0.52	41	0.59	0.89 (0.57–1.40)
Death	362	5.06	341	4.82	1.04 (0.90–1.21)
Death from cardiovascular causes	105	1.47	108	1.53	0.96 (0.73–1.25)
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)
Transfusion performed	35	0.49	31	0.44	1.11 (0.68–1.80)

* Shown are data for the intention-to-treat population (all the patients who had undergone randomization), with censoring for the ment of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation.
† Data include TIA with positive imaging.

Table 3. Clinical Outcomes (On-Treatment Population).*

Outcome	Apixaban (N=1989)		Aspirin (N=1972)		Hazard Ratio (95% CI)
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*	
Stroke or systemic embolism	36	0.71	65	1.29	0.55 (0.37–0.83)
Stroke	36†	0.71	63	1.25	0.57 (0.38–0.85)
Ischemic or unknown type	29	0.57	53	1.05	0.54 (0.35–0.86)
Hemorrhagic	8	0.16	10	0.20	0.78 (0.31–1.98)
Severity according to score on modified Rankin scale					
0–2	22	0.43	32	0.64	0.69 (0.40–1.18)
3–6	11	0.22	29	0.58	0.37 (0.19–0.75)
Missing data	3	0.06	2	0.04	1.43 (0.24–8.58)
Systemic embolism	0		2	0.04	NA
Stroke, TIA, or systemic embolism‡	53	1.04	86	1.71	0.61 (0.43–0.86)
Stroke, systemic embolism, or death from cardiovascular causes	76	1.50	94	1.87	0.80 (0.59–1.09)
Stroke, myocardial infarction, systemic embolism, or death	193	3.81	206	4.11	0.92 (0.75–1.12)
Myocardial infarction	27	0.53	33	0.66	0.81 (0.49–1.35)
Death	139	2.73	122	2.42	1.11 (0.87–1.42)
Death from cardiovascular causes	42	0.83	37	0.73	1.13 (0.72–1.75)
Major bleeding§	86	1.71	47	0.94	1.80 (1.26–2.57)
Fatal bleeding	5	0.10	8	0.16	0.63 (0.20–1.91)
Symptomatic intracranial hemorrhage	12	0.24	15	0.30	0.77 (0.36–1.64)
Gastrointestinal bleeding	45	0.89	20	0.40	2.23 (1.32–3.78)
Transfusion performed	26	0.51	18	0.36	1.43 (0.78–2.61)

* Shown are data for the on-treatment population (all the patients who had undergone randomization and received at least one do assigned trial drug), with follow-up censored 5 days after permanent discontinuation of trial medication for any reason.
† One patient in the apixaban group had both an ischemic stroke and a hemorrhagic stroke. This patient was counted once for the

Table 4. Clinical Presentation and Management of Major Bleeding.*

Variable	Apixaban	Aspirin
No. of major bleeding events	93	49
Clinical presentation — no. (%)		
1: Without emergency	11 (12)	6 (12)
2: Need for some measures	57 (61)	27 (55)
3: Hemodynamic instability or neurologic symptoms	17 (18)	13 (27)
4: Fatal	2 (2)	2 (4)
Missing data	6 (6)	1 (2)
Clinical course — no. (%)		
1: Conservative measures	21 (23)	16 (33)
2: Supportive care, transfusion	54 (58)	22 (45)
3: Immediate measures needed to avoid death	9 (10)	4 (8)
4: Death unavoidable	3 (3)	6 (12)
Missing data	6 (6)	1 (2)

* Categorization is based on classification of bleeding used in previous publications.[17,18] Percentages may not total 100 because of rounding.

Discussion

The ARTESIA trial showed that among patients with episodes of subclinical atrial fibrillation and risk factors for stroke, the risk of stroke or systemic embolism was lower by 37% (95% CI, 12 to 55) with apixaban than with aspirin, and the risk of disabling or fatal stroke was lower by 49%

The risk of major bleeding in the on-treatment analysis was increased by a factor of 1.8 (range, 1.3 to 2.6) in the apixaban group as compared with the aspirin group

In that study, the risk of ischemic stroke or systemic embolism increased from 0.69% per patient-year among patients without subclinical atrial fibrillation to 1.69% per patient-year among those with **subclinical atrial fibrillation.**

In the AVERROES trial, which involved patients with **clinical atrial fibrillation** and a mean CHADS2 score of 2 who were receiving aspirin,

we reported that the rate of stroke or systemic embolism was 3.7% per patient-year

Thus, subclinical atrial fibrillation does not appear to increase

the risk of stroke or systemic embolism to the same extent as clinical atrial fibrillation

In considering the clinical benefit of apixaban therapy in patients with subclinical atrial fibrillation, one needs to assess both the

benefits and risks.

Simply counting strokes as compared with bleeding events might suggest a neutral overall effect. With apixaban as compared with aspirin,

31 fewer cases of stroke or systemic embolism were seen in the intention-to-treat analysis, as compared with 39 more major bleeding events in

the on-treatment analysis. However, strokes involve permanent loss of brain tissue, whereas major bleeding is usually reversible, with most patients having complete recovery

In the ARTESIA trial, apixaban did not results in substantially higher rates of transfusion, fatal bleeding, hemorrhagic stroke, or other intracranial hemorrhage than aspirin.

In addition, although 45% of strokes among patients assigned to receive aspirin resulted in death or clinically significant long-term disability, nearly 90% of all major bleeding events in patients who received apixaban were managed with nonprocedural measures only (including blood transfusion)

. Only 17 of 93 episodes of major bleeding (18%) in patients assigned to receive apixaban had clinical presentation with hemodynamic instability or neurologic symptoms (13 such episodes were noted with aspirin)

Similarly, only 9 of 93 patients **(10%)** with bleeding during apixaban therapy required immediate measures to avoid death or died from bleeding (4 such patients were receiving aspirin). Thus, on the basis of the considerably greater severity of the stroke events prevented than the bleeding events caused, we believe that these findings favor consideration of the use of oral anticoagulation for patients with risk factors for stroke in whom subclinical atrial fibrillation **develops.**

The conclusions of the **NOAH-AFNET 6 trial** were that edoxaban, as compared with placebo, did not provide a benefit with respect to the primary efficacy outcome and was associated with a higher incidence of a composite of deathor major bleeding.

- ✓ the NOAHAFNET 6 trial was stopped early, had relatively few stroke events

- ✓ the primary efficacy outcome of the NOAH-AFNET 6 trial included death from cardiovascular causes. Because deaths in this population of patients are rarely due to stroke and are commonly due to underlying cardiovascular disease.
- ✓ Third, the control group in the NOAH-AFNET 6 trial was assigned to received placebo (and many received aspirin), whereas all the patients in the control group in the ARTESIA trial were assigned to receive aspirin.

2023

ARTESIA TRIAL

Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation

Randomized, Parallel, Blinded Controlled Trial

Objective: to evaluate apixaban compared with aspirin among patients with subclinical atrial fibrillation (AF).

4012 Patients

Inclusion criteria: PPM or ICD or insertable cardiac monitor capable of detecting SCAF; ≥1 episode of SCAF ≥ 6 minutes in duration but no single episode > 24 hours. SCAF requires electrogram confirmation unless ≥ 6 hours in duration. Age ≥ 55 years. CHA2DS2-VASc score ≥3

apixaban 5 mg twice daily (n = 2,015)	VS.	aspirin 81 mg daily (n = 1,997)

Primary Outcome

0.78	Stroke or systemic embolism %/person-year P=0.007	1.24

Secondary Outcomes

1.71	rate of major bleeding %/person-year P=0.001	0.94
5	Fatal bleeding (n)	8

Conclusion: Among patients with subclinical atrial fibrillation, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin but a higher risk of major bleeding.

Healey JS et al. N Engl J Med 2023;Nov 12:[Epub ahead of print].

نتیجه گیری

هدف این مطالعه استفاده از آپیکسابان در پیشگیری از سکته مغزی در بیمارانی که subclinical AF دارند می باشد.

این مطالعه روی ۴۰۰۰ بیمار انجام شده که بیماران به دو گروه تقسیم شدند. ۲۰۱۵ نفر آپیکسابان (۵۰میلی گرم دوبار در روز) و ۱۹۹۷ نفر آسپرین (۸۱ میلی گرم در روز) دریافت کردند. نتایج نشان داد که مصرف آپیکسابان باعث کاهش ۲۲ ٪ در ایجاد استروک یا آمبولی سیستماتیک می شود و همچنین ریسک خونریزی های جدی ۲۹٪ افزایش می یابد اما خونریزی کشنده تفاوت معنی داری در دو گروه نداشت.

توصیه می شود به بیمارانی که subclinical AF دارند آپیکسابان تجویز شود اما آموزشهای لازم در رابطه با علائم خونریزی و مراجعه فوری جهت درمان خونریزی داده شود

subclinical AF: به طور اتفاقی در بیماری که دستگاه ICD یا pace maker دارند یا به هر علتی مانیتورینگ قلبی می شود حداقل یک حمله ۶ دقیقه ای یا بیشتر AF دیده شود که کمتر از ۲۴ ساعت طول بکشد.